



Cover story

Enhanced immune responses by co-adsorption of liposomal adjuvant formulations to the aluminum-antigen complex



Aluminum salts, which have extremely complex mineralogical properties, were first discovered as immunostimulants in 1926, and were introduced as adjuvants for human vaccines in the 1930s [1]. In one study of 234 licensed vaccines worldwide that were examined in 2012, 146 (62%) were adjuvanted with aluminum salt [2]. Despite their extensive use, aluminum adjuvants have a few drawbacks. They have only modest potency, and they stimulate mainly antibodies (Th1-type immunity) with little, if any, cell-mediated (Th2-type) immunity. However, because they are suspensions of complex microparticles, aluminum salts have large surface areas that can serve as landing sites for other adjuvants having different types of immunostimulant properties. There are two licensed vaccines that have utilized a combination of aluminum salt with a second adjuvant. Fendrix[®] contains monophosphoryl lipid A micelles (MPL[®]) extracted from bacterial lipopolysaccharide, and recombinant hepatitis B antigen, both of which are adsorbed to aluminum phosphate. Cervarix[®] contains MPL[®] and virus-like particles from human papilloma virus, both of which are adsorbed to aluminum hydroxide. GlaxoSmithKline (GSK) introduced an adjuvant formulation containing the combination of MPL[®] micelles and aluminum salt, known as Adjuvant System 04 (AS04). GSK has also recently introduced and licensed a herpes zoster (shingles) vaccine, Shingrix[®], which contains an adjuvant formulation (AS01B) that combines three adjuvants: liposomes containing phospholipids with unsaturated fatty acids (dioleoyl phosphatidylcholine), MPL[®], and QS21, a triterpenoid glycolipid saponin derived from tree bark. The AS01B aqueous suspension is used to hydrate a lyophilized recombinant protein antigen from Herpes zoster.

The paper in this issue from the team led by Dr. Carl R. Alving at the Walter Reed Army Institute of Research [3] introduces a new concept, namely to utilize liposomes containing phospholipids with saturated fatty acids and synthetic monophosphoryl lipid A (MPLA), which is an adjuvant combination known as Army Liposome Formulation (ALF). The ALF adjuvant adsorbed to aluminum salt is known as ALFA, and ALF combined with QS21 saponin is known as ALFQ [4]. The ALF and ALFQ adjuvants were then adsorbed to aluminum hydroxide gel that contained adsorbed antigens (either gp140 HIV-1 envelope protein, or a heroin hapten conjugated to tetanus toxoid that is being developed for a heroin vaccine) to form ALFA and ALFQA, respectively. Three important observations were made. First, both ALFA and ALFQA were more potent for induction of antibodies in mice than adsorption of antigen to aluminum hydroxide alone. Second, lyophilized ALF could be reconstituted by hydration with the aluminum salt suspension to form a potent ALFA. Third, the IgG subtype and cytokine analyses after immunization with ALFA or ALFQA indicated a balanced Th1 and Th2 response, while immunization with antigen adsorbed to aluminum salt alone induced almost exclusively a Th2 immune response. Based on

these results, it is proposed that among the 146 licensed vaccines reportedly adjuvanted with aluminum salt, some might be enhanced, if beneficial to do so, by adding lyophilized ALF.

In another paper in this issue, Dr. Sergio C. Oliveira's group in Brazil describes gold nanorods as an adjuvant formulation of a recombinant protein (rSm29) derived from the tegument of adult *Schistosoma mansoni* worms [5]. There is a need for development of vaccines against parasitic diseases, such as schistosomiasis, leishmaniasis, malaria, and others, and they report that gold nanorod carriers can provide enhanced induction of Th1 immunity. Thus, this strategy might be employed for enhancement of Th1-type type immunity for vaccines to infectious diseases.

Development of new, highly effective adjuvants is urgently needed, but the progress has been slow. Developing new adjuvants is expensive, as they have to be proven safe and effective through clinical studies. While searching for new adjuvants should continue, smart use of existing adjuvants may provide alternative, more efficient approaches of developing better adjuvant systems. ALF and ALFQ adjuvants results in both Th1-type and Th2-type immunity, while gold nanorod adjuvant elicit Th1-type immunity. These studies suggest that judicious selection of adjuvants can also control the type of immune responses. The systematic studies by Dr. Carl R. Alving's and Dr. Sergio C. Oliveira's teams, contribute significantly to accelerating the search for new vaccines for important diseases, such as HIV/AIDS, parasitic infections, opioid addiction, and Alzheimer's disease.

References

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